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Review

The Complication of Severe Malaria: Focus on Black Water Fever

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Abstract:

Blackwater fever is a rare but severe complication of malaria, primarily caused by Plasmodium falciparum infection. It is characterized by the sudden onset of intravascular hemolysis, hemoglobinuria (dark or black-colored urine), fever, and often jaundice. The condition results from the massive destruction of red blood cells, often associated with repeated use of quinine-based antimalarial drugs and incomplete treatment of malaria. Clinical features may include severe anemia, renal failure, and circulatory shock, posing a high risk of mortality if left untreated.

Advancements in diagnostic tools, such as polymerase chain reaction (PCR) for malaria detection and improved renal function monitoring, have facilitated early diagnosis. Management involves prompt antimalarial therapy, fluid resuscitation, and in severe cases, blood transfusion and renal replacement therapy. Despite its declining prevalence due to improved malaria control programs and the introduction of artemisinin-based therapies, blackwater fever remains a critical concern in endemic areas. This review highlights the pathophysiology, clinical presentation, and modern approaches to managing this life-threatening condition.

KEYWORDS: Blackwater fever, malaria, Plasmodium falciparum, intravascular hemolysis, hemoglobinuria, renal dysfunction.

1.INTRODUCTION:

Blackwater fever (BWF) is a severe febrile syndrome occurring in patients with malaria, characterized by massive intravascular haemolysis and haemoglobinuria with intermittent passage of dark-coloured urine, anaemia, and possible development of acute renal failure. Although some authors attributed the description of BWF as far in time as Hippocrates, most likely BWF started to be observed at the beginning of the 19th century, coincidentally with the more widespread use of quinine Incidence was described around 0.5–2% of malaria cases and mortality around 20–35%[1].

At the turn of 19th–20th century, four main theories on the cause of BWF were discussed: (a) intoxication by quinine; (b) malaria itself; (c) consequence of previous malaria infections; and (d) an agent different from malaria. The physiopathology of BWF was still largely obscure when apparently it virtually disappeared around the Second World War, notably when antimalarial drugs other than quinine, such as mepacrine or chloroquine[2].

Children under the age of 5 years accounted for two thirds (67%)of global malaria deaths in 2018.. More than half of all cases were in six countries: Nigeria (25% of cases); Democratic Republic of the Congo (12%); Uganda (5%); Côte d'Ivoire, Mozambique and Niger (4% each). About 3.4% of all malaria cases were in the

WHO South-East Asia Region and 2% in the WHO Eastern Mediterranean Region .According to WHO 2018, there were an estimated 228 million cases compared to 231 million in 2017.The global incidence rate of malaria (number of cases per 1000 population) fell from 71 in 2010 to 57 in 2014 and remained at similar levels through. Estimated deaths due to malaria fell globally from 585 000 in 2010 to 40,5000 in 2018. However, the rate of reduction of malaria mortality was slower in the period 2016–2018 than in the period 2010–2022. Many factors seem to be involved in the occurrence of black water fever .plasmodium falciparum It causing severe hemolysis by the invasion of Red Blood cells, the enzymatic activity deviated by plasmodium and oxidative stress caused by malaria infection**.**

• Genetics: All European expatriates who used Quinine in prevention and treatment of malaria did not develop BWF. Genetic studies showed the involvement of this gene in malaria occurrence [3] **.**

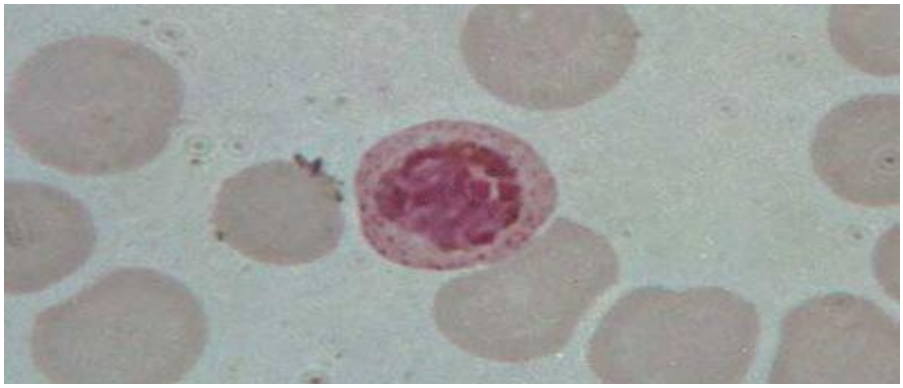


Fig:1 Causative of black water fever

BWF was first described in non-immune European expatriates who lived in endemic malaria regions .Rare in indigenous populations, the first cases have been reported in Southeast Asia and among African children in Senegal Recently, resurgence of this disease was reported in other African populations living in areas with stable malaria transmission

who are supposed to have sufficient immunity against malaria.In the Democratic Republic of Congo (DRC), BWF caused acute renal failure in children with more than 22% of mortality rate[4]**.**

The pathogenesis of BWF is complex. Inadequate malarial immunity, misuse of quinine and G6PD deficiency have been associated with the occurrence of BWF . G6PD status was already studied in DRC where the prevalence varies from 6.1% to 23.4% . The ingestion of quinine by non-immune residents affected with P. falciparum in endemic areas was associated with BWF [5–9]. Isolated cases of BWF have also been reported from patients treated with other anti-malarial drugs, such as halofantrine, mefloquine and artemether-lumefantrine**.** Resurgence of BWF is observed in many parts of the world such as Africa,

4.EPEDEMIOLOGY:

Children under the age of 5 years accounted for two thirds (67%)of global malaria deaths in 2018.. More than half of all cases were in six countries: Nigeria (25% of cases); Democratic Republic of the Congo (12%); Uganda (5%); Côte d'Ivoire, Mozambique and Niger (4% each). About 3.4% of all malaria cases were in the WHO South-East Asia Region and 2% in the WHO Eastern Mediterranean Region .According to WHO 2018, there were an estimated 228 million cases compared to 231 million in 2017.The global incidence rate of malaria (number of cases per 1000 population) fell from 71 in 2010 to 57 in 2014 and remained at similar levels through. Estimated deaths due to malaria fell globally from 585 000 in 2010 to 40,5000 in 2018[5].

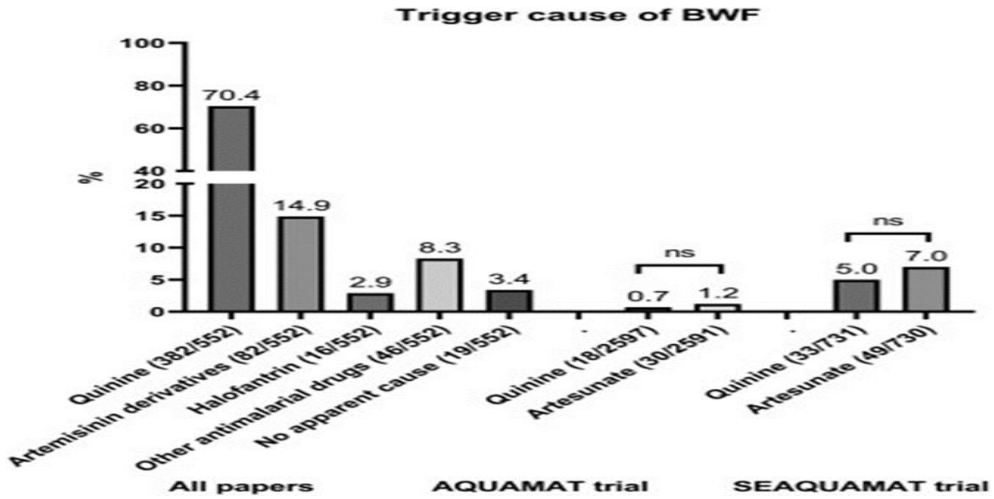


Fig:2 Trigger cause of black water fever

However, the rate of reduction of malaria mortality was slower in the period 2016–2018 than in the period 2010–2022. Many factors seem to be involved in the occurrence of black water fever.

AGENTS	**AFFECTED AREAS**
plasmodium vivax	India,Bangladesh ,Pakisthan Srilanka
Plasmodium falciparum and plasmodium vivax	South east asia,South ameria
Plasmodium falciparum	Africa, Halthi, New guenia
Plasmodium malaria	Asia, Africa
Plasmodium ovale	Africa

Table:1 Affected areas for plasmodium vivax

Plasmodium falciparum: It causing severe hemolysis by the invasion of Red Blood cells, the enzymatic activity deviated by plasmodium and oxidative stress caused by malaria infection. Malaria immunity: Malaria immunity should be involved because BWF was described firstly in none-immune population of European expatriates[6]. Autochthone populations who develop BWF have probably malaria immune deficiency exposing them to develop massive intravascular hemolysis as expatriate individuals. Measure of malaria IgG is necessary to explore this issue[7].

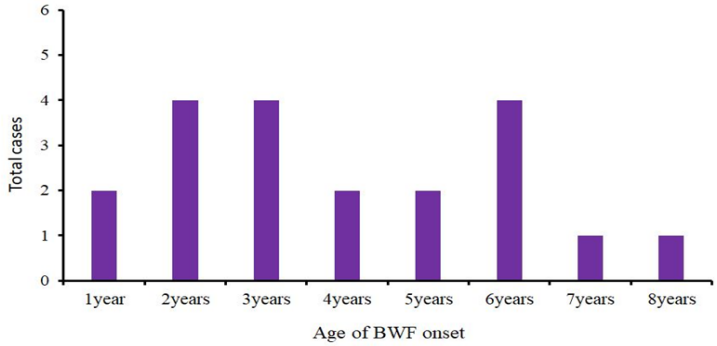


Fig:3 Total cases of black water fever regarding to age[8]

Species	Incubation period
Plasmodium falciparum	9-14 days
Plasmodium malaria	18-40 days
Plasmodium vivax	8-17 days
Plasmodium ovale	16-18 days

Table 2 : Incubation period for plasmodium species[9]

5.ETIOLOGY:

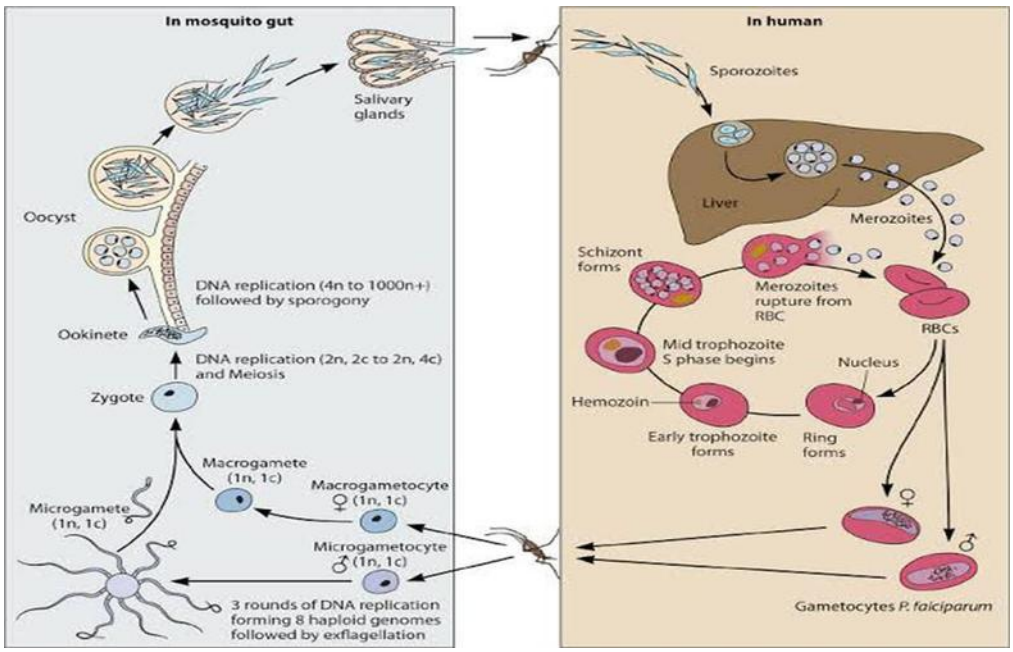


Fig:4 Pathogenesis of plasmodium vivax

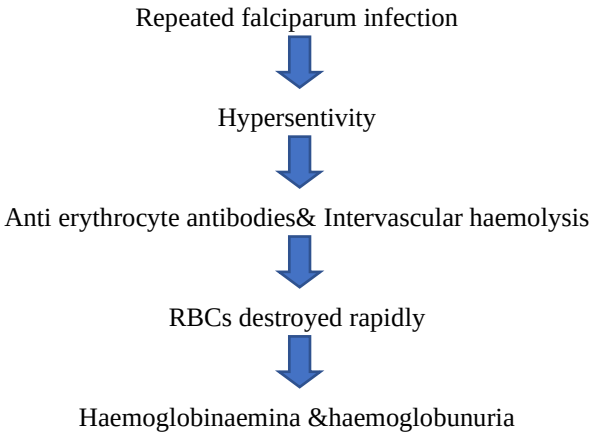
- **Other drugs**: Toxemia from drugs can cause blackwater fever
- **Severe infection:** Severe infections can cause blackwater fever.
- **Poisons**: Organic and inorganic poisons can cause blackwater fever.
- **Burns**: Burns can cause blackwater fever.

Five species of genus *Plasmodium* are known to cause malaria in humans. The vector for *Plasmodium spp.* is a female A*nopheles* mosquito that inoculates sporozoites contained in her salivary glands into the puncture wound when feeding. Sporozoites enter peripheral bloodstream and are up taken by hepatocytes, where they undergo an asexual pre-erythrocytic liver-stage as liver schizonts lasting up to 2 weeks before the onset of the blood stage. As they replicate within hepatocytes, they form motile merozoites that are subsequently released into the bloodstream, where they invade red blood cells (RBC).[10]

6.PATHOPHYSIOLOGY:

The rupture of the first liver schizont and the release of motile merozoites into peripheral circulation to invade red blood cells marks the start of a possible symptomatic infection. The first rupture and invasion are usually silent in most infected patients, but as the asexual cycle repeats itself in the next 24 to 48 hours, parasitemia rises, and immune response increases accordingly. It is usually associated with an increase of TNF alpha and other inflammatory markers in the cascade, including interleukin 10 (IL-10) and interferon-gamma (IFN-

gamma).Higher parasitemia's are generally associated with a more severe clinical picture, but the relationship is very variable[11].



7. CLINICAL&MANIFESTIONS:

Urine: is a made up of water and waste products that is produced by the kidneys ,stored in the bladder ,and excreted through the urethra.

- Chills :chills and fever are often associated with each other and are a natural response to infections and other illnesses.
- Fever: A fever is the fever natural response to infections and other conditions .viruses and bacteria multiply poorly above 98.6 F, which is the average human body temperature.
- kidney damage: Acute kidney injury serious complications of black water fever .Hemoglobin released from lysed red blood cells can obstruct the renal tubules ,leading to renal failure.
- Hemodynamic instability: Due to the severe anemia and fluid stifts ,patients may develop hypotension .shock multi organ failure.
- Acute kidney injury : occurs when the kidneys are unable to filter waste products from the blood, causing a buildup of urea and creatinine. This can lead to electrolyte and fluid imbalances, and can affect other organs[12].

8. PREVENTION :

Malaria can be prevented by avoiding mosquito bites and by talking medicines Talk to a doctor about talking medicines such as chemoprophylaxis before travelling to areas where malaria is common Lower the risk of getting malaria by avoiding mosquitoes bites :

- Use mosquito nets when sleeping places where malaria is present .
- Use mosquito repellents after dusk .
- Use coils and vaporizers .
- Wear protective clothing.
- Use window screens. Preventing blackwater fever primarily involves strategies to prevent malaria, especially P. falciparum infections**.**

1. Malaria Prophylaxis: Using appropriate prophylactic anti-malarial drugs when traveling to high-risk areas.
2. Insecticide-Treated Mosquito Nets: Reducing mosquito bites is key in preventing malaria transmission.
3. Insect Repellents and Protective Clothing: Using DEET-based repellents and wearing long sleeves can further protect against mosquito bites.

9. DIAGNOSTIC TESTS:

presenting symptoms, but can be supported by laboratory findings:

1. Blood Smear: Identification of P. falciparum parasites in a stained blood smear under a microscope.

2. Urine Analysis: Presence of hemoglobin or myoglobin in the urine without red blood cells.
3. Blood Tests:
Hemoglobin Levels: Typically very low due to hemolysis.
Blood Levels: Elevated indirect bilirubin due to red blood cell breakdown.
Kidney Function Tests: Elevated blood urea nitrogen (BUN) and creatinine levels indicating renal impairment[13].

10.TREATMENT:

He management of blackwater fever involves both supportive care and specific treatment aimed at controlling the underlying malaria infection**.**

Pharmacological Treatment:

1.Antimalarial medications: Artemisinin-based combination therapies (ACTs) are the first-line treatment for Blackwater fever.
2 .Quinine: Quinine is an alternative treatment option, but it can exacerbate treatment
3.Exchange transfusion: In severe cases, exchange transfusion may be necessary to remove damaged red blood cells.
4. Dialysis: Dialysis may be necessary to manage acute kidney injury.
5. Antibiotics: Antibiotics may be prescribed to prevent or treat secondary bacterial infections.

Non-Pharmacological Treatment:

1. Rest and hydration: Rest and hydration are essential to manage the symptoms of Blackwater fever.
2. Blood transfusion: Blood transfusion may be necessary to replace damaged red blood cells.
3. Dietary modifications: Dietary modifications such as avoiding fava beans and other oxidative stress-inducing foods may be recommended.
5. Psychological support: Psychological support and counseling may be necessary to manage the emotional and psychological impact of Blackwater fever[13].

Traditional and Alternative Medicine.

1. Herbal remedies: Herbal remedies such as Artemisia annua and Cinchona officinalis have been traditionally used to treat malaria and Blackwater fever.
2. Acupuncture: Acupuncture may be used to manage pain and discomfort associated with Blackwater fever.
3. Homeopathy: Homeopathic remedies such as China and Natrum muriaticum may be used to manage the symptoms of Blackwater fever.

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11.CONCLUSION

Blackwater fever is a rare but life-threatening complication of malaria, characterized by intravascular hemolysis, hemoglobinuria, and acute kidney injury. This review highlights the complex pathophysiology, clinical presentation, and management strategies for Blackwater fever.Despite advances in malaria treatment and control, Blackwater fever remains a significant challenge in endemic regions. The condition is often associated with high morbidity and mortality, particularly in areas with limited access to healthcare.

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